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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,273	06/19/2003	Susan J. Braunhut	08688-057001 / UML 02-06	6439

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EXAMINER	
SCHUBERG, LAURA J	

ART UNIT	PAPER NUMBER
1657	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/601,273	BRAUNHUT ET AL.	
	Examiner	Art Unit	
	Laura Schuberg	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 21-46* is/are pending in the application.

4a) Of the above claim(s) *11-15 and 21-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/02/2007 has been entered.

Election/Restrictions

Claims 1-15 and 21-46 are pending.

Claims 21-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions there being no allowable generic or linking claim.

Newly amended claims 11-15 are also withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected specie (bioactive fragments of the ECM), there being no allowable generic or linking claim. Election was made **without** traverse of growth factors, specifically fibroblast growth factor, in the reply filed on 04/13/2006.

Claims 1-10 have been examined on the merits.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-6, and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Mitchell et al (US 6,962,814 B2).

Amended claim 1 is now drawn to a method of generating a morphogen composition from an extracellular matrix, the method comprising: growing cells on a surface under conditions and for a time sufficient to enable the cells to form an extracellular matrix (ECM); removing living cells from the surface and leaving the ECM on the surface, wherein the cells remain intact upon removal; stimulating the extracellular matrix to release morphogens into the fluid; and collecting the fluid to form a morphogen composition. Dependent claims are drawn to wherein the morphogens are growth factors or differentiating factors (growth factors elected), wherein the morphogen composition comprises a plurality of morphogens, wherein the fluid comprises a biocompatible liquid or gel, and further includes wherein the ECM is substantially free of living cells.

Amended claim 6 is now drawn to a method of generating a morphogen composition from an extracellular matrix comprising: growing cells on a surface under conditions and for a time sufficient to enable the cells to form an extracellular matrix

(ECM); removing living cells from the surface and leaving the ECM on the surface, wherein the cells remain intact upon removal; applying an electric potential to the extracellular matrix to release morphogens into the fluid; and collecting the fluid to form a morphogen composition.

According to M.P.E.P. § 2111, the pending claims must be given their broadest reasonable interpretation consistent with the specification. Broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. In *In re Prater* (citations omitted), the court ruled that "reading a claim in light of the specification, to thereby interpret limitations explicitly recited in the claim, is a quite different thing from reading limitations of the specification into a claim,' to thereby narrow the scope of the claim by implicitly adding disclosed limitations which have no express basis in the claim. It is also stated that it is improper to read a specific order of steps into method claims where, as a matter of logic or grammar, the language of the method claims did not impose a specific order on the performance of the method steps, and the specification did not directly or implicitly require a particular order.

Therefore, Applicant's claims as written, given their broadest reasonable interpretation consistent with the specification, do not require a specific order to the method steps.

Mitchell teaches a method that involves growing cells to produce an extracellular matrix, applying electrical stimulation to the culture (cells and matrix), and decellularization (column 8 line 31-line 41, lines 65-67). Decellularization with proteases (such as trypsin) which allow for the cells to be removed intact is also taught (column 19

lines 3-5). Upon removal of the cells from the matrix, the morphogen composition, produced by the electrical stimulation of the matrix, is also inherently collected.

Therefore, the teachings of Mitchell inherently anticipate Applicant's invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-5 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rieck et al (Experimental Cell Research 1995) in view of Livesey et al (US 5,336,616).

Rieck teaches a method of extracting fibroblastic growth factor 2 (FGF2) from an ECM by growing endothelial cells, dissolving the cell layer with Triton X-100, exposing

the subendothelial matrix, and extracting the FGF2 with either 2M NaCl or trypsin thus forming a morphogen composition with fibroblast growth factor and a biocompatible fluid (page 37-column 1 last paragraph- column 2).

Rieck does not teach wherein the cells remain intact upon removal.

Livesey teaches a method for processing and preserving an acellular collagen-based tissue matrix (abstract). Livesey also teaches that decellularization can be accomplished using a number of chemical treatments, including incubation in certain salts, detergents (Triton X-100) or enzymes (trypsin) (enzymatic removal would leave the cells intact). Livesey also teaches that with care, cellular removal with enzymes may occur without significant damage to the extracellular matrix (column 9 lines 41-67).

Therefore, it would have been obvious for one of ordinary skill in the art to modify the method of Rieck to substitute the step of cell removal with detergent treatment (Triton X-100) with cell removal by trypsinization because Livesey teaches that these methods are art recognized equivalents for cell removal while leaving the extracellular matrix substantially intact (column 9 lines 41-67). Also, the trypsin method would also have the added benefit of allowing the practitioner of subculturing the intact cells for further use, which the dissolving method with detergent (Triton X-100) would not allow. One of ordinary skill in the art would have had a reasonable expectation of success because both Rieck (page 37) and Livesey (column 4 line 33) were concerned with the selective preservation of the matrix after cell removal.

Therefore, the combined teachings of Rieck and Livesey render obvious Applicant's invention as claimed.

Claims 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rieck et al (Experimental Cell Research 1995) and Livesey et al (US 5,336,616) as applied to claims 1-5 and 10 above, and further in view of Koyama et al (Nature Biotechnology 1997) and Simpson et al (US 2002/0090725 A1).

Claims 7-9 are dependent upon claim 6.

Claim 7 further includes wherein the electric potential cycles from negative voltage to a positive voltage and back to a negative voltage. Claim 8 further includes wherein the electric potential ranges from –0.3 V to +0.3 V. Claim 9 further includes varying frequency, potential range, potential cycle shape, or potential cycle number of the electric potential to control release and activation of specific morphogens.

Rieck and Livesey combined teach a method of generating a morphogen composition from an extracellular matrix as described above.

Rieck does not teach wherein stimulating the ECM comprises applying an electric potential to the ECM.

Koyama teaches that electrical stimulation markedly promoted the nerve growth factor (NGF) secretion from astroglial cells (page 165 column 1 lines 19-22).

Simpson teaches that an electrical field can stimulate movement or conformational changes in a matrix due to the movement of magnetically or electrically sensitive particles. Such movement can affect the release of compounds from an electroprocessed matrix. Simpson also teaches that electroprocessed material may be

induced to release substances (such as growth factors) (page 27 para 223). Simpson further teaches that altering the conformation of the matrix can increase or decrease the extent to which the material is favorable for compound release.

Therefore, one of ordinary skill in the art would have been motivated to use an electric potential to stimulate the secretion of growth factors in the ECM in the method of Rieck because Koyama teaches that electrical stimulation promotes growth factor secretion from cultured cells (which include an ECM) and also because Rieck shows that there is more than one way to extract growth factor from an extracellular matrix (page 37 column 2, line 6). Additional motivation would have been provided by Simpson because Simpson shows that electrical stimulation of the matrix also affects release of compounds from the matrix (page 26 para 222 and page 28 para 230). The modulation of the electric potential to comprise varying frequency, potential range, potential cycle shape or potential cycle number would have been a matter of routine optimization for one of ordinary skill in the art. The artisan recognizing that the optimum electric potential cycle and voltage would produce the greatest amount of cell growth and/or growth factor secretion. One of ordinary skill in the art would have had a reasonable expectation of success because Simpson teaches that an electrical field can stimulate movement or conformational changes in a matrix due to the movement of magnetically or electrically sensitive particles (page 28 para 230).

Therefore, the combined teachings of Rieck, Livesey, Koyama and Simpson render obvious Applicant's invention as claimed.

Response to Arguments

Applicant's arguments filed 03/02/2007 have been fully considered but they are not persuasive. The arguments have been addressed in so far as they relate to the new grounds of rejection above.

Applicant argues that Koyama's focus is using electrical potential to induce astroglial cells growing on the electrode to produce and secrete NGF. Given this focus, Applicant asserts that one skilled in the art, at best, would have been motivated to apply a potential to living cells, which would produce and secrete NGF. Applicant asserts that Koyama teaches away from the claimed method since Koyama focuses on inducing living cells and not ECM to produce NGF.

This is not found persuasive because Koyama's teaching combined with that of Simpson's gives evidence that the ECM when treated with an electric field will release growth factors. Simpson's teaching gives evidence of the release of compounds from the ECM upon treatment with an electric field and Koyama's teaching gives evidence that these compounds (which are secreted by the cells along with the ECM proteins and stimulated to release by an electric field) are growth factors. Therefore, one of ordinary skill in the art would know based on Simpson's teaching of the effect of electrical stimulation on the ECM that the growth factor secreted in the electrical stimulation process of Koyama was also provided by the stimulated ECM as well as the stimulated cells. In other words, both Simpson and Koyama provide information that would lead

one of ordinary skill in the art to use electrical stimulation on an ECM to provide release of growth factors.

Applicant argues that Simpson's method focuses on incorporating bioactive material into a collagen matrix (which can be used as a vehicle to deliver the bioactive materials into a tissue). Applicant asserts that this is the opposite of the claimed method which obtains a morphogen from an ECM and thus one of skill in the art would not have had a reasonable expectation of success in combining the references to obtain morphogens from an ECM.

This is not found persuasive because Simpson is a supporting reference to the primary reference of Rieck and provides the reassurance that a collagen matrix can be induced to release compounds by electrical stimulation as well as the other forms of stimulation as taught by Rieck. Simpson's teachings encompass several embodiments for the use of electroprocessed collagen (including the use of an extracellular matrix) (abstract) and specifically teaches that variations can be made to produce a wide variety of electroprocessed materials and substances (page 17 para 158). Clearly Simpson did not intend to limit the application of electroprocessed collagen. Simpson clearly provides evidence that materials, such as growth factors (page 9 para 98) can be released from an extracellular by electrical stimulation. The combination of references is reasonable since Rieck, Koyama and Simpson are all concerned with the manipulation of cells, ECM and the growth factors produced.

Applicant argues that the man-made collagen matrix described in Simpson is quite different from an ECM as recited in the claimed invention, which is much more

complex. Applicant asserts that in view of this complexity, one skilled in the art would not have a reasonable expectation of success of using the Simpson method for man-made collagen matrix to induce morphogens to be released from the ECM described in Rieck.

This is not found persuasive because Simpson specifically teaches that the collagen matrix to be electroprocessed would include those from a natural source as well as those produced synthetically (page 6 para 77). Simpson teaches that natural sources include, but are not limited to, collagens produced by or contained within the tissue of living organisms (page 6 para 77). Clearly the collagen matrix of Simpson would therefore include embodiments that would have a comparable complexity with that taught by Rieck or claimed by Applicant.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura Schuberg whose telephone number is 571-272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leon B Lankford, Jr
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Laura Schuberg